Effects of being imitated on motor responses evoked by pain observation: Exerting control determines action tendencies when perceiving pain in others.

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Abstract

Brain imaging research has shown that experiencing pain oneself and perceiving pain in others lead to a similar pattern of activation, suggesting that the latter is based on internal simulation of the observed pain. Further evidence for this idea stems from transcranial magnetic stimulation measuring corticospinal excitability (CSE). It has been demonstrated that our motor cortex is involved whenever we observe another person receiving painful stimulation to the hand (e.g. Avenanti, Bueti, Galati, & Aglioti, 2005). However, both decreases and increases of CSE have been described during pain observation. Hence the exact nature of these CSE changes has remained unclear so far. In the present study, we hypothesized that CSE changes are determined by the control that the observer has over the hand that receives painful stimulation. To test this hypothesis, we manipulated the control over the observed hand using a paradigm in which participants' movements are being imitated by a hand on screen – giving them full control over the hand – or not. In accordance with previous results, we evidenced a decrease in CSE when participants experienced no control over the hand that received painful stimulation. In contrast, inducing control resulted in an increase in CSE. We conclude that exerting control over the observed hand leads to a completely altered action tendency. Whereas an anaesthetic response is typically observed in the absence of control, increasing control induces motor facilitation reminiscent of preparation of an avoidance response.

Since the study of Singer et al. (2004), it has been repeatedly shown that the observation of pain in a model results in pain-related brain activation in the observer (for a review see Lamm, Decety, & Singer, 2011). More recently, transcranial magnetic stimulation (TMS) studies have investigated how our motor system responds when perceiving pain in others. Interestingly, these studies have shown that the observation of painful stimulation delivered to the hand of a human model induces a *decrease* in corticospinal excitability (CSE) in the hand of the observer (e.g. Avenanti, Bueti, Galati, & Aglioti, 2005; Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2006). It has been argued that this inhibitory effect is similar to what happens on the motor level when experiencing pain oneself (e.g. Farina, Tinazzi, Le Pera, & Valeriani, 2003; Le Pera et al., 2001; Urban et al., 2004). However, recent findings indicate that the decrease in CSE observed while perceiving pain in others is not always found. It has been shown that this inhibition is reduced in individuals with high levels of trait-personal distress (Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2009). Furthermore, Fitzgibbon et al. (2012) have shown that pain synesthetes (i.e. individuals who experience actual pain when observing injury to another) show a significant *increase* in CSE while observing pain in others. These discrepant results raise questions about the factors that determine the nature of CSE changes induced by pain observation. A potential hypothesis is that, in experiments demonstrating an anaesthetic motor inhibition after painful stimulation, participants were unable to avoid the pain or predict the exact timing of painful stimulation (e.g. Le Pera et al., 2001; Urban et al., 2004). Similarly, in experiments where participants perceive pain in others, the decrease in CSE is typically associated with an absence of control over the hand in pain. On the other hand, high levels of personal distress or synesthetic sensations may enhance the feeling that pain is inflicted on one's own hand and activate motor control processes, resulting in increased CSE as a reflection of planning an avoidance reaction to the observed pain. In the present study, we tested the original hypothesis that the nature of the CSE changes evoked by perceiving others' hand receiving painful stimulation is determined by our ability to exert control over this hand.

We recently manipulated the sense of control participants had over an observed hand in pain using a well-established imitation paradigm (De Coster, Verschuere, Goubert, Tsakiris, & Brass, 2013). In an imitative condition a hand on screen imitated participants, giving them perfect control over this hand. In a non-imitative condition, the hand was performing non-matching movements. We showed that affective reactions to perceiving painful stimulation in others were enhanced after being imitated by the other person and that this enhancement was related to an increase in control. In the present study, this imitation paradigm allowed us to investigate whether inducing control over the hand on screen determines whether perceiving pain in this hand will lead to increased or decreased CSE.

Materials and Methods

Participants

Twenty-five healthy young adult men (mean age = 22.44 years, SD = 2.03) participated in the study in exchange for 40 Euros, and provided written consent beforehand. All participants had no history of neurological or psychiatric disorders, had normal or corrected-to normal vision, and were negative for the risk factors associated with TMS (Rossi et al., 2009). The procedures were non-invasive and were performed in accordance with the ethical standards laid down in the 1964 Helsinki Declaration. The study was granted ethical approval by the Medical Ethical Review Board of Ghent University Hospital.

Experimental design

Blocks of trials consisted of two phases: an action phase in which movements of the subjects were imitated (exerting control block) or not (not exerting control block), and a pain perception phase which immediately followed the action phase. In the pain perception phase, one of ten pain movies was presented (*'bore goes into the back of the hand'*, *'hammer is smacked on the back of the hand'*, *'hot iron is pressed on the back of the hand'*, *'knife cuts the back of the hand'*, *'nail is knocked into the back of the hand with a hammer'*, *'nail of the ring finger is pulled out of the hand'*, *'paper makes a paper cut in the back of the hand'*, *'pinchers pinch the back of the hand'*, *'sandpaper is rubbed over the back of the hand'*, *'stapler puts a staple into the back of the hand'*), or a neutral movie was shown in which a still hand appeared on screen, serving as a baseline for the pain movies. Each pain movie was combined two times with both an exerting control and not exerting control block, while the neutral movie was combined 20 times with each block to ensure that an equal amount of pain and neutral movies was presented. As such, the experiment consisted of 80 trials. The association of the different pain/neutral movies with the different block conditions was completely randomized across participants.

Stimuli and apparatus

Stimulus material consisted of three types of 720 x 576 video-clips created by professionals: a hand in a resting position, simple finger movements (for the action phase of the task), and pain movies showing a hand receiving pain stimulation (for the pain movies in the pain perception phase).

During the action phase of the experimental task, participants carried out simple finger movements of the index, middle, ring, or little finger. These finger movements were recorded with a custom-built response device using light sensors. This device allowed us to use finger lifting movements of participants as triggers for the presentation of the appropriate finger movement video. Temporal resolution was optimized (see Procedure) so that participants immediately viewed a video-taped finger movement on screen after initiating a finger movement with their own hand. For example, in an exerting control block, the lifting of an index finger resulted in the presentation of the index finger lifting video, while the middle, ring, or little finger lifting video was shown in a not exerting control block. All finger movement clips had a total duration of 2000 ms.

The perception phase of the experimental task consisted of the presentation of one of ten pain movies in which painful stimulation was applied to the hand on screen, or a resting state movie in which the right hand was displayed palm down with fingers slightly spread. The position of the video-taped hand matched the position of the participants' right hand on the response box. All movies had a total duration of 8000 ms. The resting state movie served as a neutral/baseline movie for the pain movies (Avenanti et al., 2009). Practical constraints (including timing of the experiment) detained us from using additional control conditions in which hands are innocuously touched by similar objects. While several studies have shown that CSE is modulated by observation of pain but not of touch stimuli (e.g. Avenanti et al., 2005, Avenanti, Sirigu, & Aglioti, 2010) we cannot exclude the possibility that our modulations are not specific for pain and can be extended to any hand-object interaction.

Procedure

Participants were seated in front of a standard computer screen at arm length, and asked to place the four fingers of their right hand on a custom-made response box. Display of stimulus material and recording of responses were conducted with Presentation software

(Neurobehavioral Systems, Inc.). As soon as the video-taped right hand appeared on screen (resting state movie), subjects were instructed to voluntary move a randomly chosen finger that was placed on the response box. Immediately after movement of one of the subjects' fingers (delay = 0 ms, estimate of intrinsic delay of computer/software = 66.93 ms), a movie was shown in which the hand on screen performed the same or a different movement for exerting control and not exerting control blocks respectively. After a random number between 10 and 15 of such movements (all imitative or all non-imitative), one of the pain movies or the neutral movie was immediately presented. After a pain movie, participants had to rate the behavioural statement 'I felt pain on my own hand when I saw the hand on screen receiving painful stimulation' on a scale from -5 to +5. During the pain movies, a TMS pulse was applied at the exact time when the painful tool contacted the skin surface. During the neutral movie, the TMS pulse was delivered at 2900 ms, corresponding to the average of the TMS pulse onset across all pain movies.

Before the start of the experiment, participants' TMS motor threshold was measured as described in the TMS and Electromyography paragraph below. Afterwards, they performed two practice blocks (both an exerting control and a not exerting control block), in which a pain movie was shown that was not used during the experimental phase and no TMS pulse was applied. During these practice blocks, it was verified whether participants understood all aspects of the experimental procedure.

Finally, at the end of the experiment, participants filled in the Interpersonal Reactivity Index (IRI; Davis, 1980; for Dutch translation see De Corte et al., 2007), used as a measure of trait empathy. This questionnaire consists of 28 items which have to be rated on a 5-point Likert scale, and can be divided into four subscales: Perspective Taking (PT, the tendency to spontaneously imagine and assume the cognitive perspective of another person), Empathic

Concern (EC, the tendency to feel sympathy and compassion for others in need), Fantasy (FS, the tendency to project oneself into the place of fictional characters in books and movies), and Personal Distress (PD, the extent to which an individual feels distress as a result of witnessing another's emotional distress). Cronbach's α in the current study for PT was .83, for EC .74, for FS .79, and for PD .80.

TMS and Electromyography

Single pulse TMS was delivered through a biphasic magnetic stimulator (Rapid^2 Magstim, Whitland, UK) connected to a polyeruthane-coated figure-of-eight coil (5.4-cm inner diameter windings). The coil was held tangentially over the left hand motor area, with the handle pointing backwards and forming an angle of 45° with the sagittal plane. Participants wore earplugs to attenuate the coil noise. Electromyographical (EMG) activity was recorded with the ActiveTwo system (BioSemi, Amsterdam, The Netherlands). Sintered 11 x 17-mm active Ag–AgCl electrodes were placed over the right First Dorsal Interosseus muscle (FDI) and the right Brachioradialis muscle (BR) in a belly–tendon arrangement. The FDI contributes to flex or abduct the index away from the middle finger, whereas the main action of the BR is to flex the forearm at the elbow. These muscles were chosen because they are involved, respectively, in finger and hand retraction, two reactions commonly observed in response to painful stimuli as used in our study. The hot spot in the hand motor area was established by locating a stimulation site where TMS elicited motor evoked potentials (MEPs) in the two muscles. TMS intensity was set at 110 % of the resting motor threshold, i.e. the minimum intensity to induce an MEP ≥ 50 μV peak to peak in both muscles with 50 % probability. In 14 out of 25 participants, the TMS parameters were defined according to the FDI only because it was not possible to elicit MEPs in both muscles from the same stimulation site. The data collected from the BR in other participants were excluded from further analyses because the number of trials where an MEP was observed during the experiment was too small. Average intensity (± S.D.) was 71.25 (± 16.98) % of the maximal stimulator output. EMG signal was amplified (internal gain scaling), digitized at 2 kHz, high-pass filtered at 3 Hz, and stored on a PC for off-line analysis.

Data analyses

Trials were excluded when the root mean square (RMS) of the background EMG signal recorded in the FDI 500 ms before TMS was higher than 50 μV. For each subject, the top and bottom 5% of MEPs were trimmed and the peak-to-peak amplitude of the remaining MEPs was computed using Matlab. For both control conditions separately, the MEPs in each pain condition were expressed as a percentage of change with respect to its corresponding baseline as follows: 100 * (Pain – Neutral)/Neutral. The baseline conditions did not differ significantly from each other, $t(24) = 1.34$, $p = .20$.

Planned comparisons between exerting control and not exerting control over the observed hand were performed for behavioural and TMS data using paired *T*-tests. For the latter, additional analyses were performed to rule out that the effects described in the Results section were due to differences in background EMG activity. These analyses showed that our manipulation did not influence the RMS of the EMG signal recorded from the FDI during a 500 ms delay before the TMS (all *p*-values >.20).

Pearson correlations were computed between the average ratings on each subscale of the IRI and the percentage of change in MEP amplitude in the exerting control and not exerting control conditions. One outlier participant was identified using Cook's distance and subsequently removed from the correlation analysis.

Results

Subjective Reports

In accordance with previous results (De Coster et al., 2013), a paired *T*-test revealed that scores were significantly higher in the exerting control compared to the not exerting control condition: $t(24) = 2.31$, $p < .05$, $d = .15$ (see Figure 1).

Insert Figure 1 about here

TMS data

Planned comparisons of the percentage of change in MEP amplitude in the FDI showed a significant difference between the exerting control and not exerting control condition: $t(24) = 3.44$, $p < .01$, $d = 1.87$. As shown in Figure 2, MEP amplitude decreased in the not exerting control condition (one –sample *T*-test against 0: $t(24) = -2.29$, $p < .05$, $d = .93$), replicating previous findings (e.g. Avenanti et al., 2005, 2006). In contrast, MEP amplitude increased in the exerting control condition (one –sample *T*-test against 0: $t(24) = 2.63$, $p < .05$, $d = 1.07$).

Insert Figure 2 about here

Correlations were computed between the average rating of each subscale of the IRI and the percentage of change in MEP amplitude, averaged for the exerting control and not exerting control condition separately. A negative relationship was found between PT and MEP amplitude in the not exerting control condition (r = -.60, p < .01; see Figure 3a). In other words, participants who were more likely to cognitively infer others' states showed a stronger inhibition at the motor level. Furthermore, a positive relationship was found between PD and MEP amplitude in the exerting control condition (r = .53, p < .01; see Figure 3b), meaning that participants who were more likely to feel distressed about seeing someone else suffering showed a stronger motor facilitation. No other correlations were found between subscales of the IRI and the change in MEP amplitude in the exerting or not exerting control condition (all ps > .05).

Insert Figure 3 about here

Discussion

In this TMS experiment, we investigated whether action tendencies evoked by painful stimuli delivered to the hand of a human model depend on the ability to exert control over the observed hand. Subjects observed the hand of another person receiving painful stimulation, after being imitated by this hand or not. During the pain perception phase, TMS-induced MEPs were measured in the right dominant hand of participants. In accordance with previous results, we showed that when participants did not exert control over the hand that received painful stimulation (i.e. incongruent movements), decreased CSE was found during pain observation. By contrast, when participants exerted control over the hand that received painful stimulation (i.e. congruent movements), increased CSE was observed.

It has been repeatedly shown that observing others in pain does not only generate affective but also sensory-motor responses in the observer (Keysers, Kaas, & Gazzola, 2010; Lamm et al., 2011). Indeed, several TMS studies exploring reactions to perceiving pain in others evidenced decreased excitability in the motor system of the observer. This decrease has been shown to be specific to the body part that was hurt in others and to correlate with the pain intensity as estimated by the observer (e.g. Avenanti et al., 2005, 2006; Minio-Paluello, Avenanti, & Aglioti, 2006). It has been argued that this inhibition reflects a freezing response that is similar to the reaction observed when actually experiencing pain (e.g. Farina et al., 2003; Le Pera et al., 2001; Urban et al., 2004). Other research, however, has shown that high levels of personal involvement are associated with reduced motor inhibition during pain observation (Avenanti et al., 2009). Moreover, Fitzgibbon et al. (2012) have shown that pain synesthetes show a significant increase of CSE when observing someone else in pain. The current study accounts for these discrepancies by showing that action tendencies are modulated by the level of control participants exerted over the hand that received painful stimulation.

Several TMS studies have shown that increased CSE might reflect anticipatory changes to perception of negative emotional cues (Oliveri et al., 2003; Koganemaru, Domen, Fukuyama, & Mima, 2012; Borgomaneri, Gazzola, & Avenanti, 2013). Furthermore, it has been shown that the motor system implements anticipatory simulations of expected actions (Avenanti, Annella, Candidi, Urgesi, & Aglioti, 2013; Borroni, Montagna, Cerri, & Baldissera, 2005; Kilner, Vargas, Duval, Blakemore, & Sirigu, 2004; Urgesi et al., 2010). We assume that the facilitation of CSE observed in the exerting control condition reflects planning of an avoidance reaction to the observed pain. In particular, this increased CSE might reflect an unspecific muscle tension halting ongoing behaviour in order to prepare for a potential avoidance response. Such an avoidance response is only adaptive when the agent has the possibility to escape the painful stimulation. Previous studies examining CSE when experiencing pain oneself used methods (e.g. saline injection, electrical stimulation) that prevent preparation of appropriate reactions to avoid pain (e.g. Le Pera et al., 2001; Urban et al., 2004). In such situations where it is already too late to stop or avoid the painful stimulation, an anaesthetic motor inhibition is the most adaptive response. By definition, situations in which participants passively observe pain to the hand of a human model preclude an active avoidance response, and thus anaesthetic motor inhibition is displayed. In a previous study, De Coster et al. (2013) showed a reduced sense of agency when the hand that receives pain does not imitate the finger movements executed by participants. In this sense, the "not exerting control" condition is similar to observing others in pain without any possibility to prepare an avoidance reaction to this pain. In support of this view and in line with previous research (Avenanti et al., 2009; Avenanti et al., 2010; Minio-Paluello, Baron-Cohen, Avenanti, Walsh, & Aglioti, 2009), a correlation was found in our study between this inhibitory effect and the individual ratings of perspective taking, a cognitive marker of empathy, in the not exerting control condition. It seems that the more a participant feels able to cognitively change his/her perspective to adopt others' point of view, the more he/she experiences motor inhibition during pain observation. Interestingly, Shamay-Tsoory, Aharon-Peretz, and Perry (2009) suggested that perspective taking is closely related to Theory of Mind abilities and the awareness that others' states are different from one's own. By contrast, being imitated provides participants with a feeling of control over the model hand, due to an increased self-other overlap (De Coster et al., 2013). The more participants are distressed about seeing the hand that they can control, the more they show activation in this hand. This correlation is in accordance with Borgomaneri et al. (2013) who found that inter-individual differences in personal distress were positively correlated with an increased CSE. Interestingly, facilitory CSE responses when viewing negative stimuli seem to be muscle unspecific (e.g. Borgomaneri et al., 2013). This raises the possibility that facilitation of CSE might be part of a more generalized preparatory response towards negative situations, especially since Borgamaneri et al. (2013) indicated the very early nature of these facilitory responses. This might indicate that the first response to a threatening situation is a complete and unspecific muscle tension that serves the role of stopping ongoing behaviour and preparing avoidance. Unfortunately, we were not able to test this hypothesis because the data from the only other muscle we measured (the BR muscle) were not reliable.

In accordance with previous results (De Coster et al., 2013), we showed that behavioural self-reports of pain intensity were higher in the exerting control condition compared to the not exerting control condition. Furthermore, in this previous study both other- and self-oriented feelings were rated higher in the exerting control condition, reflecting concern and personal distress respectively (Batson, Fultz, & Schoenrade, 1987). In addition, we found that not only agency/control was higher in the imitation condition, but that this condition elicited higher body ownership as well. In particular, we demonstrated that exerting control induced a rubber hand illusion (RHI) indicating enhanced body ownership (De Coster et al., 2013). It is therefore an open question whether the effect of exerting control directly influenced the action tendency or whether this effect is mediated by increased body ownership. In any case, our study is the first experimental study showing increased CSE in a situation where self-other overlap is high. While it has been shown using fMRI that threatening a rubber hand that feels as if it is your own hand increases brain activity in pain-related and motor-related areas (Ehrsson, Wiech, Welskopf, Dolan, & Passingham, 2007), the specific nature of the motor response (inhibition or facilitation) cannot be investigated with fMRI. Interestingly, other research (Schütz-Bosbach, Mancini, Aglioti, & Haggard, 2006; Schütz-Bosbach, Avenanti, Aglioti, & Haggard, 2009) has shown that when applying motor TMS in a RHI paradigm (without observation of noxious stimulation), differential modulation of the FDI was present as well. While asynchronous stimulation (no RHI) led to increased MEP amplitude and reduced cortical silent period duration when observing index finger movements, synchronous stimulation (RHI) led to the opposite pattern. These results confirm the idea that self-other overlap can modulate CSE, reflecting appropriate responses to the observed stimuli.

In addition, our study provides the first systematic evidence that CSE changes induced by pain observation are mediated by the merging of self-other representations. Although it has been widely accepted that the inhibitory effect is due to an embodiment of the observed pain, this has never been systematically demonstrated. With the current paradigm we demonstrated that CSE effects in the "exerting control" condition are qualitatively different from those in the "not exerting control" condition. Our study thus suggests that increasing self-other overlap (due to being imitated in the "exerting" condition) leads to a facilitation of MEPs when observing pain, and that this facilitation is higher for people who are more strongly affected by other's distress. As such, these results indicate that being imitated has a strong influence both on emotional reactions, such as empathy for pain, and bodily reactions in the observer. Enhancing self-other overlap by being imitated thus provides a novel and original paradigm for investigating pathological populations, such as autism or schizophrenic individuals, who show altered emotional reactions that are related to deficiencies in self-other representations (e.g. autism, schizophrenia).

In sum, our results indicate that whether we exert control over an observed body part or not determines the nature of the CSE changes consecutive to perceiving pain in others. While having no control leads to motor inhibition when observing someone in pain, exerting control leads to motor facilitation. We argue that this increase in CSE response reflects the tendency to prepare for avoidance of the painful stimulation. By contrast, having no control over the hand rather elicits an anaesthetic response, as evidenced by motor inhibition.

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Figure 1. Mean scores on the question *'I felt pain on my own hand when I saw the hand on screen receiving painful stimulation'* (range from -5 to +5) in the exerting control and not exerting control condition after observing a pain movie. Error bars are standard errors of the mean.

Figure 2. Mean CSE in the exerting control and not exerting control, computed as the percentage change compared to baseline [100 * (Pain – Neutral)/Neutral]. Error bars are standard errors of the mean.

Figure 3. A. Correlation between mean IRI Perspective Taking (PT) score and mean CSE in the not exerting control condition. B. Correlation between mean IRI Personal Distress (PD) score and mean CSE in the exerting control condition.